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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/316,199	05/21/1999	Michael J McCluskie	C1040/7006HC	7506

7590 05/26/2010

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EXAMINER	
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ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
05/26/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/316,199	MCCLUSKIE ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-9,12,13,15-20,22,25-28,129,135-142 and 144-146* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-9,12,13,15-20,22,25-28,129,135-142 and 144-146* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/10/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/09/2010 has been entered.

Claims 2, 3, 10, 11, 14, 21, 23, 24, 29-128, 130-134 and 143 have been cancelled.

Claims 1, 4-9, 12, 13, 15-20, 22, 25-28, 129, 135-142 and 144-146 are pending and under examination.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a

nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1, 5-9, 12, 15-18, 22, 129, 135-137, 139-142 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4, 5, 9-11, 13 and 14 of copending Application No. 10/300,247. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claims are drawn to a method of inducing a mucosal immune response by administering to a subject an oligonucleotide 8 to 100 nucleotides long and a viral antigen not encoded by a nucleic acid; the oligonucleotide has the formula 5' $X_1X_2CGX_3X_4$ 3', wherein C is unmethylated, X_1, X_2, X_3, and X_4 are nucleotides, and both the oligonucleotide and the antigen are administered intranasally or ocularly (claims 1, 22, 129, 135-137, and 139-142). The antigen is delivered in colloidal dispersion systems (claims 5-7), the method further comprises administering a non-oligonucleotide adjuvant, such as MPL (claims 8 and 9), the subject is at risk of developing an infectious disease (claim 12), the oligonucleotide contains phosphorothioate modifications at the 5' end or the 3' end (claims 15-17), X_1X_2 could be GpT and X_3X_4 could be TpT (claim 18). The specification defines that the viral antigen could be a hepatitis B viral antigen and

therefore, the vaccine could be used to elicit an immune response in a subject infected with hepatitis B therefore, i.e., the vaccine can be used to treat a subject infected with hepatitis B (p. 27, lines 14-23, p. 29, line 14, p. 40, lines 13 and 14).

The application claims recite a method of treating a subject infected with hepatitis via inducing an immune response against hepatitis virus by administering to the subject an oligonucleotide 8 to 100 nucleotides long, an antigen, and a non-nucleic acid adjuvant (claims 1, 4, and 12), wherein the non-nucleic acid adjuvant could be MPL (claim 5); the oligonucleotide has the formula 5' $X_1X_2CGX_3X_4$ 3' wherein C is unmethylated, X_1, X_2, X_3, and X_4 are nucleotides, the oligonucleotide contains phosphorothioate modifications at the 5' end or the 3' end (claims 9-11 and 13), X_1X_2 could be GpT and X_3X_4 could be TpT (claim 14). The specification defines that the antigen could be a polypeptide (i.e., not encoded by a nucleic acid vector), the non-nucleic acid adjuvant could be a liposome (i.e., micellar, lipid-based system), and that the delivery could be intranasal or ocular (p. 3, lines 11 and 12, p. 16, lines 5-13, p. 27, lines 16 and 17). Although the application claims do not recite a mucosal immune response, such is inherent to the application method. This is because the oligonucleotide recited in the application claims is identical to the instant oligonucleotide and therefore, its intranasal or ocular delivery necessarily results in a mucosal immune response.

Since the application claims embrace all the limitations of the instant claims, the application claims and the instant claims are obvious variants.

Applicant states that the rebuttal of the provisional double patenting rejection is deferred until the cited co-pending application is allowed.

Applicant's statement is acknowledged; however, the rejections will be maintained until a Terminal Disclaimer is filed or claims are amended to obviate the rejection.

4. Claims 1, 4-9, 12, 13, 15-20, 22, 25-28, 129, 135-142 and 144-146 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-22 of the U.S. Patent No. 7,488,490 (filed as Application No. 10/023,909), in view of Craig (U.S. Patent No. 6,689,757, of record). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

The claims are obvious variants because both claim sets encompass a method of inducing mucosal immune response via administering to a subject a composition comprising an antigen, an oligonucleotide having the formula 5' $X_1X_2CGX_3X_4$ 3', wherein C is unmethylated and X_1, X_2, X_3, and X_4 are nucleotides, and a non-oligonucleotide adjuvant such as MPL. The patent specification defines that delivery could be intranasal, rectal or vaginal (see column 32, lines 47-50). Although the patent claims do not specifically recite a mucosal immune response, such is inherent to the application method. This is because the oligonucleotide recited in the patent claims is identical to the instant oligonucleotide and therefore, its intranasal, rectal, or vaginal delivery necessarily results in a mucosal immune response. The patent claims do not

recite further using B-7, as recited in the instant claim 25. Craig teaches using B-7 to upregulate the immune response to vaccines (column 6, lines 35-49). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the patent claims by further using B-7 costimulatory molecule, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to enhance the immune response elicited against the vaccine of interest. One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that B-7 can be successfully used to potentate the immune responses to antigens.

Thus, the instant claims and the patent claims are obvious variants.

The applicant argues that the examiner has incorrectly stated in the Office Action at page 7 that "the type of immune response depends on the administration route." The examiner provides no basis or substantiating evidence for this proposition. Based on this incorrect assumption, the examiner concludes that the patent specification teaches mucosal delivery and mucosal delivery necessarily results in mucosal immune response. Again, the Examiner provides absolutely no basis or substantiating evidence for this conclusion. The applicant notes that various references of record indicate otherwise. For example, in Grdic et al., an antigen-adjuvant composition induced a systemic immune response after being administered orally (Grdic et al. Eur. J. Immunol., 29:1774-1784, 1999). In Ugozzoli et al., an antigen-adjuvant composition generated a fecal immune response after being administered intramuscularly.

Significantly, Ugozzoli et al. failed to generate a mucosal immune response when another antigen- adjuvant combination was administered intranasally (Ugozzoli et al. Immunol., 93:563-571, 1998). These references refute the Examiner's position that "mucosal delivery necessarily results in mucosal immune response."

The applicant argues that the examiner is using hindsight by applying the teachings that are found only in the instant application (i.e., that CpG oligonucleotides are able to induce a mucosal immune response). Nothing in the '490 patent teaches that a CpG oligonucleotide induces a mucosal immune response, and nothing in the '490 patent teaches a subject that is in need of a mucosal immune response. These claim limitations are also not obvious to one of ordinary skill in the art. The teachings of Craig do not cure the deficiencies in the '490 patent claims.

Finally, an obviousness rejection cannot be based on that which is unknown at the time of the invention. In re Rijckaert, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). The instant application is the first disclosure of the ability of CpG oligonucleotides to generate a mucosal immune response when administered to a mucosal site. This activity was unknown prior to the invention. The instant claims, which recite induction of a mucosal immune response in a subject in need of a mucosal immune response, would not have been obvious to one of ordinary skill in the art at the time of the invention based on the claims of the '490 patent because it was not known, nor could it have been reasonably expected, prior to the invention that CpG oligonucleotides could induce mucosal immunity.

The applicant's arguments are acknowledged; however, they are not found persuasive for the following reasons:

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to the applicant's argument that the capability of CpGs to generate a mucosal immune response was unknown prior to the invention, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Specifically, since the CpG oligonucleotide recited in the patent claims is identical to the instant CpG oligonucleotide, its delivery to a mucosal site necessarily results in a mucosal immune response. Therefore, the patent claims do not have to specifically recite a mucosal immune response; such would naturally flow from using the method recited in the patent claims. For these reasons, the argument that the teachings of Grdic et al. and Ugozzoli et al. refute the position that the intranasal administration of the patented CpG oligonucleotide necessarily results in an immune

response is not found persuasive. The references (which are of record) are immaterial to the instant rejection because they do not relate to CpG oligonucleotide, but rather to adjuvants such as cholera toxin, ISCOM, MF59, PLG microparticles, and LT-K63.

For the reasons set forth above, the rejection is maintained.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 4-9, 12, 13, 15-20, 22, 25-28, 129, 135-142, and 144-146 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al. (U.S. Patent No. 6,239,116, of record) in view of each Agrawal et al. (U.S. Patent No. 6,426,334, of record), Briles et al. (U.S. Patent No. 6,042,838, of record), Craig (U.S. Patent No. 6,689,757, of record), and Kincy-Cain et al. (Infection and Immunity, 1996, 64: 1437-1440, of record).

Krieg et al. teach a method of inducing an immune response in a subject by orally administering to the subject an oligonucleotide 8 to 100 nucleotides in length, wherein the oligonucleotide can be administered by itself or concurrently with an antigen; the oligonucleotide has a sequence which includes the formula 5' $X_1X_2CGX_3X_4$ 3' wherein C is unmethylated, X_1, X_2, X_3, and X_4 are nucleotides, the oligonucleotide contains phosphorothioate modifications at the 5' end or the 3' end, X_1X_2 could be GpT,

and X_3X_4 could be TpT (claims 1, 4, 15-18, 136-139, and 141) (Abstract, column 6, lines 1-67, column 7, column 14, lines 3-32, column 28, lines 4-25, column 45, lines 36-42, column 46, lines 55-60). Krieg et al. teach that the administration of the oligonucleotide by itself results in an immune response; such an immune response would protect a subject from subsequent passive exposure to antigen (claim 138) (columns 6, lines 38-51). Krieg et al. teach that a non-oligonucleotide adjuvant could be included in the immunogenic composition (claim 8), that the antigen could be a protein, i.e., not encoded by a nucleic acid vector (claims 1, 20, 136, 137, 139, 141, 142, and 144-146) (column 7, lines 1-7, column 9, lines 48-53), and that the method could be used to induce an immune response in subjects to eliminate tumors or viral infections (claims 12, 13, 135, and 140) (column 10, lines 23-61). Krieg et al. teach administering the composition in conjunction with liposomes (claims 5-8) (column 13, lines 40-45, column 45, lines 6-17). Krieg et al. teach their oligonucleotide as having the formula 5' TCCATGTCGTTCCTGTCGTT3' (SEQ ID NO: 73), i.e., comprising the sequence 5' $TCNTX_1X_2CGX_3X_4$ 3' wherein N is 2 (claim 19) (column 32, Table 10). Krieg et al. also teach boosting with oligonucleotide to enhance the immune responses to the vaccines (claim 27) (column 47, lines 10-29). The limitation of inducing a mucosal immune response is inherent to the method of Krieg et al. because all that is required to achieve such is to administer their oligonucleotide to a mucosal site. With respect to the limitation recited in claim 28, it would have been obvious to one of skill in the art to include the non-nucleic acid adjuvant in the boost in order to improve the results.

Krieg et al. do not teach specifically the recited routes of administration recited in the instant claims 1, 136, 137, 139 and 141. However, at the time of filing such administration routes were taught by the prior art. For example Agrawal et al. teach inducing an immune response by administering oligonucleotides having a sequence including the claimed formula via intranasal or rectal administration (claims 1, 136, 137, 139, and 141) (column 5, lines 30-45, column 6, lines 48-50). It would have been obvious to one of skill in the art, at the time the invention was made, to substitute the oral administration of Krieg et al. with the intranasal or rectal administration of Agrawal et al. to achieve the predictable result of inducing immunity. The limitation of the intranasal immunization resulting in mucosal immunity at remote sites (claim 26) is an inherent feature of their method because all that is required to achieve such is to intranasally administer their oligonucleotide.

Although Krieg et al. and Agrawal et al. teach the use of non-nucleic acid adjuvants, they do not specifically teach the adjuvants recited in claim 9. However, at the time the invention was made, such adjuvants were well known and used in the prior art. For example Briles et al. teach the use of saponins or cholera toxin and its B subunit (column 4, lines 20-30, column 8, lines 14-18). It would have been obvious to one of skill in the art to use an adjuvant such as cholera toxin in the method of Krieg et al. and Agrawal et al. to achieve the predictable result of eliciting an immune response.

Krieg et al., Agrawal et al., and Briles et al. do not teach administering B-7 costimulatory molecule (claim 25). Craig teaches using B-7 to upregulate the immune response to vaccines (column 6, lines 35-49). Therefore, it would have been obvious to

one of skill in the art, at the time the invention was made, to modify the method of Krieg et al., Agrawal et al., and Briles et al. by further using B-7 costimulatory molecule, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to enhance the immune response elicited against the vaccine of interest. One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that B-7 can be successfully used to potentate the immune responses to antigens.

With respect to the limitation recited in claim 129, it is noted that Krieg et al. teach their oligonucleotide as being capable of inducing IL-12 (column 6, lines 1-51, column 35, lines 50-67). The prior art teaches that IL-12 induces mucosal immune responses against intracellular pathogens and it is useful as a mucosal adjuvant for vaccines used to prevent or treat infectious with pathogens which gain entry via a mucosal surface (see Kincy-Cain et al., Abstract, p. 1437, column 1, second paragraph, p. 1439, column 2). Based on these teachings, one of skill in the art would have known that the oligonucleotide of Krieg et al. is a mucosal adjuvant which could be used to treat subjects in need of mucosal immunization.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

The applicant argues that neither Krieg et al. nor Agrawal et al. teach a method of inducing a mucosal immune response.

The applicant argues that it would not have been obvious to substitute the administration routes recited by Krieg et al. with those of Agrawal et al. because neither reference teaches induction of mucosal immunity, and therefore such induction would not be predictable. One of ordinary skill in the art would not have a reasonable expectation that the methods of these references would induce mucosal immunity. Accordingly, there can be no predictability relating to the induction of mucosal immunity. That CpG oligonucleotides are able to induce a mucosal immune response when administered to a mucosal surface was not known prior to the invention. An obviousness rejection cannot be based on that which is not known prior to the invention. In re Rijckaert, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993).

With respect to Briles et al., the applicant argues that their teachings are not so broad. Briles et al. teach that "mice can be effectively immunized by intranasal (i.n.) instillation of bacterial protein immunogens, particularly when conjugated to or mixed with cholera toxin (CT) or its B subunit (CTB)." (See column 8 lines 15-18). Briles et al. further report that "when CTB is used as an adjuvant for i.n. immunizations, specific IgA antibodies are induced in secretions of the intestinal, respiratory, and genital tracts." (See column 8 lines 18-21). Accordingly, Briles et al. are emphasizing the effects of CT and CTB. These statements cannot be reasonably interpreted as teaching that intranasal administration of any antigen with any adjuvant would result in mucosal immunity at remote sites. As evidence, Ugozzoli et al. shows that not every antigen/adjuvant combination yields such results. (Ugozzoli et al. Immunol., 93:563-571, 1998). Ugozzoli et al. report that, when the HSV antigen gD2 is administered

intranasally with adjuvant MF59 or adjuvant Iscomatrix, mucosal immunity above that achieved with antigen alone is not detected in nasal washes (i.e., locally) or in saliva, vaginal and/or fecal washes (i.e., remotely). The results of Ugozzoli et al. refute the Examiner's statement.

The examiner further relies on Briles for the teaching of saponin, CT and CTB adjuvants and concludes that it would have been obvious to use such adjuvants in the methods of Krieg et al. and Agrawal et al. "to achieve the predictable result of eliciting an immune response." As stated above, since neither Krieg et al. nor Agrawal et al. teaches induction of a mucosal immune response, there is no basis to conclude that such a result would be predictable. It was not known prior to the invention that CpG oligonucleotides induce a mucosal immune response when administered to mucosal surfaces. The Examiner has provided no rationale for why such a result would have been predictable prior to the invention.

The examiner states that one of ordinary skill in the art would have known, based on the teachings of Kincy-Cain et al., that CpG oligonucleotides were mucosal adjuvants. Kincy-Cain et al. states that IL-12 can augment a mucosal immune response that arises after administration of intracellular pathogen S. dublin. The reference provides no data to evidence mucosal immune response induction, and instead infers mucosal immunity based on overall survival of the experimental subjects. The reference further speculates that IL-12 "most probably" exerts its effects through non-antigen-specific mechanisms including through IFN-gamma production by innate immune cells such as NK cells. Nothing in this reference evidences that IL-12 induction

is necessary for mucosal immune response induction or, more importantly, that CpG oligonucleotides when administered to a mucosal surface are able to induce a mucosal immune response. The examiner continues to look predominately to the teachings of Kincy-Cain et al. in spite of the teachings of other references of record which show that mucosal immunity can be achieved independent of IL-12. More specifically, Applicant has brought to the examiner's attention a number of references that teach that IL-12 may not influence a mucosal immune response and/or that the role of IL-12 in this regard may vary depending on the route of administration. Some of these references indicate that mucosal immune responses occur even in the absence of IL-12. Simmons et al. (J. Immunol. 2002, 168:1804-1812) reports that IL- 12 knockout (IL-12p40"/') mice mount gut-associated IgA responses after infection with C. rodentium. (See, for example, Figure 6). The reference further reports that only a small fraction (10-15%) of the IL-12 knockout mice died post-infection, indicating that mice are able to clear the infection independent of IL-12. The reference concludes that gut-associated IgA responses are not defective in IL-12 deficient mice. Arulanandam et al. (Vaccine 1999, 17:252-260) states that "(T)here is little information about the influence of IL-12 on mucosal immunity." (See page 252, second column, second paragraph). In support of this statement, the reference indicates that others have reported that intratracheal administration of IL-12 inhibits antigen-specific IgA in bronchoalveolar lavage (citing Yang et al. Nature Med. 1995 1:890-3) and that oral administration of IL-12 enhances serum IgG and has no effect on fecal IgA (citing Marinaro et al. J. Exp. Med. 1997 185:415-427). Arulanandam et al. itself reports no change in lung IgA levels and

suppressed fecal IgA levels in mice immunized intranasally with DNP-OVA with cholera toxin B subunit and IL-12. The reference therefore shows that presence of IL-12 at a mucosal site does not induce mucosal IgA, and it further states that "only parenteral administration of IL-12 results in enhanced faecal IgA antibody levels." Marinaro et al. (J. Immunol. 1999, 162:114-121) documents that intranasal administration of IL-12 had no effect on mucosal secretory IgA responses to oral or nasal vaccines. In response to the teachings of these references, the examiner has indicated that "just because the evidence of record indicates that intranasally-administered IL-12 does not induce a mucosal antibody response, does not mean that IL-12 cannot induce a mucosal immune response." The applicant argues that Briles, a reference made of record by the examiner, clearly states that "the principal determinant of specific immunity at mucosal surfaces is secretory IgA (s-IgA) which is physiologically and functionally separate from the components of the circulatory immune system." Accordingly, it was recognized in the art that s-IgA production was a defining marker of a mucosal immune response. The examiner further states that, based on the teachings of Krieg et al., one would have understood that CpG oligonucleotide administered orally to a subject would induce parenteral IL-12 and this in turn would induce a mucosal immune response. Even assuming that IL-12 was necessary and sufficient for inducing a mucosal immune response, there is no indication in Krieg et al. that orally administered CpG oligonucleotide would generate sufficient levels of IL-12 to induce a mucosal immune response. At most, Krieg et al. states that "the ability of a CpG ODN to induce IL-12 secretion is a good measure of its adjuvant potential, especially in terms of its ability to

induce a Th1 immune response, which is highly dependent on IL-12." (See column 35 lines 51-54). A Th1 immune response is not a mucosal immune response. However, as shown by the art of record, IL-12 is not necessary and sufficient for the induction of a mucosal immune response. Moreover, as demonstrated by Krieg et al., CpG oligonucleotides modulate the production of a number of cytokines and the activation of a variety of cells. Given the various *in vivo* effects caused by CpG oligonucleotides, and given the art-recognized uncertainty as to the role of various factors in mucosal immunity induction, there was no knowledge or any reasonable expectation by one of ordinary skill in the art that CpG oligonucleotides induce mucosal immunity when administered at a mucosal site, prior to the instant invention.

The applicant's arguments are acknowledged; however, they are not found persuasive for the following reasons:

In response to the applicant's argument that the capability of CpGs to generate a mucosal immune response was unknown prior to the invention, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Since the CpG oligonucleotide of Krieg et al. is identical to the instant CpG oligonucleotide, its delivery to a mucosal site necessarily results in a mucosal immune response. Therefore, Krieg et al. and Agrawal et al. do not have to specifically indicate that administering their oligonucleotide to a mucosal site induces a mucosal immune

response; this is inherent to their method and therefore, it would naturally flow from using their method. For the same reasons, the arguments regarding Briles et al. and Ugozzoli et al. are not found persuasive. The references are immaterial to the instant rejection because they do not relate to CpG oligonucleotide, but rather to adjuvants such as cholera toxin, ISCOM, MF59, PLG microparticles, and LT-K63.

The argument that it would have been unpredictable that using the saponin of Briles et al. would result in an immune response is just an argument not supported by any evidence. Adjuvants (such as saponin) are well-known for their capability to enhance and not inhibit the immune response. The method of Krieg et al. and Agrawal et al. already elicit an immune response and clearly saponin would not inhibit the elicited immune response. With respect to inducing a mucosal immune response, such is inherent to the method of Krieg et al. and Agrawal et al.

The arguments regarding Kincy-Cain and the references provided by the applicant used to support his arguments are not new and were previously addressed. It is noted that the references provided by the applicant only teach that IL-12 is not necessary for inducing IgA. The applicant argues that Briles et al. teach that IgA production is a marker of a mucosal immune response. But so is the induction of the mucosal CTLs (i.e., IgA induction is not the only marker of a mucosal immune response). The fact that Briles et al. do not teach CTL does not mean that that the induction of mucosal CTL is not a marker. Like any immune response, the mucosal immune response comprises both an antibody and a CTL response. The prior art teaches that mucosally-administered IL-12 acts as an adjuvant to induce the mucosal

CTL response (i.e., a mucosal immune response) and suggests using substances capable of stimulating endogenous IL-12 production to enhance the mucosal immune response when needed (Belyakov et al., of record; see Abstract, p. 1709, p. 1713, column 1). Based on these teachings in the art and since Krieg et al. teach that the orally administered CpG is capable of inducing IL-12, one of skill in the art would have known that the method of Krieg et al. results in a CTL mucosal response. The applicant argues that a Th1 response is not a mucosal response. This is incorrect. If the antigen/CpG is administered at a mucosal site, the Th1 responses take place at the mucosal site (i.e., it is a mucosal Th1 response); it is the mucosal Th1 response that induces the mucosal CTL response (see Belyakov et al., Abstract, p. 1709, p. 1713, column 1). The applicant argues that the CpG of Krieg et al. induces other cytokines beside IL-12. In response, it is noted that Krieg et al. teach induction of IL-12, IFN-γ, and GM-CSF, all being Th1 cytokines. In other words, Krieg et al. teach that their CpG is capable of inducing a Th1 response, which is consistent with the teachings in the art that a Th1 response is necessary to induce the mucosal CTL response. Therefore, there is no uncertainty and one of skill in the art would have known that the CpG of Krieg et al. is capable of inducing a CTL mucosal immune response when administered to a mucosal site. For this reason, one of skill in the art would have known and be motivated to use the method of Krieg et al. and Agrawal et al. to treat subjects in need of a mucosal immune response, as recited in the instant claim 129.

For the reasons set forth above, the rejection is maintained.

7. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Ileana Popa/
Primary Examiner, Art Unit 1633